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EXAMINER	
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DATE MAILED: 05/01/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/161,680	Applicant(s) Bornscheuer et al.
	Examiner Kathleen Kerr	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 3/12/01

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1, 2, 4-7, 10, and 11 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1, 2, 4-7, 10, and 11 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on March 12, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/161,680 is acceptable, and a CPA has been established. An action on the CPA follows.

Application Status

2. A preliminary amendment was filed on March 12, 2001 which amended Claims 1, 10, and 11. Claims 1-2, 4-7, and 10-11 are pending in the instant application and will be examined in this Office action. The Examiner notes that the "clean copy" of the pending claims at the end of Applicants' amendment incorrectly included Claims 8-9 which have been canceled in Paper No. 13 received on October 16, 2000.

Claim Objections

3. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 limits the bacteria to all kinds of bacteria, namely Gram positive or Gram negative. Moreover, fungi and yeasts are not excluded. Thus, Claim 4 in no way further limits the parent Claim 1.

4. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. This rejection was previously made in prosecution and is maintained herein; Applicants arguments have been fully considered but are not deemed persuasive for the reasons below. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim limits the alteration in substrate specificity (i.e., the new substrate which is used) to be a substrate which is different from the original substrate by virtue of its regioselectivity, its chemoselectivity, or its stereoselectivity. These three concepts define all the ways in which a substrate, or compound, can be distinct from another compound. See also 112, second paragraph rejection below.

Applicants argue that factors, such as higher activity and better binding, can also be functions of alteration of substrate specificity. While the Examiner does not disagree, these concepts are within the scope of the types of substrates now used by the "new" enzyme.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-2, 4-7, and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. In line 2, the term "affinity" is defined as k_{cat}/K_m; this definition is repugnant to the well-known definition in the art. As shown in the attached excerpt from Fersht, k_{cat} is a catalytic constant which is indicative of the rate of the enzyme's reaction, K_m is an apparent dissociation constant which is indicative of affinity, and k_{cat}/K_m is a second order rate constant which is indicative of the enzyme's catalytic rate at less-than-saturating conditions; the term k_{cat}/K_m is also referred to as a "specificity constant". While Applicants may be their own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See M.P.E.P. 7.34.02 and In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947).

b. In lines 2-3, the phrase "rises from zero or almost zero, to greater than zero" is confusing since an affinity greater than zero can be less than an affinity of almost zero. The Examiner is aware than Applicants are trying to more appropriately claim their invention to avoid the prior art; however, this phrase is not definite and is confusing. Appropriate correction is required.

c. In line 3, the phrase "converts the new substrate" is unclear. First, the enzyme should concert ---a new substrate---. Second, the verb convert indicates a product while none is indicated in the claim.

d. In line 11, the phrase "on or in" is unclear. In the art, enzymes are described as having activity in a medium or on a substrate.

Appropriate correction is required.

6. Claims 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The confusing claim language of Claim 1, particularly with respect to affinity and substrate specificity terms, requires the Examiner to interpret Claims 10-11 as best as possible in light of the specification. The Examiner has read the instant claims as limiting the "new" substrate to be a regio-, chemo-, or stereoselective isomer of the original substrate of the enzyme based on examples in the specification; however, this interpretation is not clear from the wording of Claims 10-11. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 4-7, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Greener et al. The instant claims are drawn to methods of altering the substrate specificity of an enzyme, wherein a new k_{cat}/K_m of the enzyme with respect to a substrate is generated, said method comprising (1) transforming a mutator strain with a gene encoding an enzyme, (2) incubating the strain so that the gene is mutated, (3) transferring the mutated gene to a bacterial, fungal or yeast microorganism without any impeding enzyme activity, (4) incubating said microorganism with an enzyme substrate to recognize altered substrate specificity, and (5) selecting a microorganism containing the enzyme with altered substrate specificity. Additionally, the instant claims are drawn to methods wherein the above steps are iterated. Additionally, the instant claims are drawn to methods wherein the enzyme is a phosphatase (which is an esterase). The concept of using a "new" substrate in screening, although implied in the claim language and specified Applicants' remarks, is not considered a limitation in the instant rejection based on the confusing language in Claim 1.

Greener et al. teach the introduction of a cloned phosphatase gene into the *E. coli* strain XL1-Red (Stratagene, La Jolla, CA) for the purpose of introducing single, random point mutations into said gene, iterating the process for several generations to achieve the appropriate degree of mutation in said gene, and screening for phenotypic variants of said gene in a nonmutator host organism, specifically *E. coli* which is a Gram-negative bacterium (see pages 383-384). The cloned gene specifically used in Greener et al. is alkaline phosphatase which is generally classified in the hydrolase family of enzymes (Enzyme Commission number EC 3.),

further classified as an esterase, and as such specifically meets applicants' limitations in claims 5-7. Greener et al. also teach that "[p]resumably, these...mutations [as induced by the mutator strain method] result in a variant having higher specific activity..." (see page 384); this presumption is considered a reasonable conclusion by the Examiner. The term "specific activity", as is well-known in the art and is defined by Fersht, is k_{cat}/K_m. Thus, the method taught by Greener et al. produces an esterase/phosphatase with a new substrate specificity.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 4-7, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greener et al. in view of Wilks et al. The instant claims are drawn to subject matter as described above with the proviso that the instant rejection is specifically drawn to the concept of making an enzyme which utilizes a "new" substrate and screening with said "new" substrate for enzymatic activity, even though such a limitation is not clear in the claims.

Greener et al. teach as described above. Greener et al. do not teach the step of screening the mutated phosphatase with a "new" substrate.

Wilks et al. teach achievements in protein engineering by using random mutagenesis and rational design. Particularly, on page 564, Wilks et al. teach the directed (not random) alteration of *B. stearothermophilus* lactate dehydrogenase from using an NADH substrate to using a "new" NADPH substrate. Also on page 564, Wilks et al. teach the directed (not random) alteration of a glutathione reductase from using an NADPH substrate to using a "new" NADH substrate. These examples particularly evidence the ability to engineer a "new" enzyme substrate specificity with a chemoselective alteration, that is the chemical makeup of the substrate has been changed.

It would have been obvious to one of ordinary skill in the art to practice the methods taught by Greener et al. and alter said methods to include a step of screening for "new" enzyme substrate specificities because Wilks et al. clearly teach the ease with which "new" specificities are generated, either by directed or random mutagenesis. While the examples taught by Wilks et al. result from directed mutagenesis, the random methods of Greener et al. would reasonable produce the same result given the appropriate amount of experimentation. One would have been motivated to combine the above references and assay the mutant phosphatases of Greener et al. with "new" substrates because "new" substrate specificities are useful "for the purpose of making them [enzymes] more suitable for the chemoenzymic synthesis of single compound drugs" (see Wilks et al., Abstract). One would have a reasonable expectation of success that such phosphatases would have been produced because Wilks et al. identify several examples of mutated enzymes changing substrate specificity, as noted above.

9. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greener et al. in view of Wilks et al. The instant claims are drawn to methods of altering the substrate specificity of an enzyme as described above wherein the new enzyme substrate is a stereoisomer of an original enzyme substrate.

Greener et al. teach as described above. Greener et al. do not teach the ability of the mutated phosphatase to use a "new" substrate. Greener et al. also do not disclose their method resulting in a stereoselective enzymatic activity.

Wilks et al. teach as described above. Wilks et al. also teach the engineering of a double mutant of alcohol dehydrogenase which is altered from utilizing only a single isomer of 2-octanol to using both stereoisomers (see page 563 and Creaser et al. abstract).

It would have been obvious to one of ordinary skill in the art to practice the methods taught by Greener et al. and alter said methods to include assaying for "new" enzyme substrate specificities because Wilks et al. clearly teach the ease with which "new" specificities are generated, either by directed or random mutagenesis. While the examples taught by Wilks et al. result from directed mutagenesis, the random methods of Greener et al. would reasonable produce the same result given the appropriate amount of experimentation. One would have been motivated to combine the above references because "new" substrate specificities are useful "for the purpose of making them [enzymes] more suitable for the chemoenzymic synthesis of single compound drugs and other **chiral** compounds" (emphasis added) (see Wilks et al., Abstract). One would have a reasonable expectation of success that chirally-specific enzyme would have

been produced because Wilks et al. identify a specific example of a mutated enzyme altering the stereo-selectivity of the utilized substrate, as noted above.

Response to Arguments of Art Rejections

10. The Examiner responded to Applicants' arguments concerning the objection to Claim 10 above. Applicants' arguments concerning the 102(b) and 103(a) art rejections of record are addressed below.

Applicants traverse the rejection of Claims 1-2 and 5-7 under 35 U.S.C. 102(b) as anticipated by Greener et al. This rejection has been maintained above with the proviso that the limitation of using a "new" substrate is unclear; Claims 4 and 10 (which are objected to as not further limiting Claim 1) have also been included in the rejection above. A 103(a) rejection has also been set forth above in anticipation of Applicants' amendments to Claim 1 to clarify the concept of a "new" substrate.

Applicants argue that the Examiner has misunderstood the meaning of the phrase "alteration of substrate specificity". The Examiner will reiterate that this phrase is interpreted, considering the well-known definitions in the art as noted in Fersht, as a change in the quantitated value of k_{cat}/K_m. Applicants use the term "affinity" and "substrate specificity" interchangeably or incorrectly, and these incorrect definitions are repugnant to well-known definitions in the art. The Examiner notes that Fersht describes well-known definitions in the art of the enzymology as the following:

$\mathbf{k_{cat}}$ = catalytic rate constant (turnover number) measuring how fast the enzyme can catalyze a reaction maximally (at saturating conditions)

$\mathbf{K_m}$ = the dissociation constant measuring the affinity an enzyme has for a particular substrate (at saturating conditions)

$\mathbf{k_{cat}/K_m}$ = second order rate constant (specificity constant) measuring the reaction rate at less-than-saturating conditions.

These definitions *cannot* be redefined by Applicants in their specification, and in turn their claims, because such re-definition would cause great confusion in claim interpretation.

Applicants argue that the Examiner has not considered the fact that Claim 1 is drawn to a method of making an enzyme having a "new" substrate specificity (or affinity) wherein the enzyme, mutated by Applicants' method, now utilizes a substrate which is not utilized by the non-mutated enzyme. Applicants argue that Greener et al. do not teach producing an entirely "new" enzyme substrate specificity. The Examiner notes that the term "new" must be considered a relative term, considering the art. While a particular enzyme may not convert (catalyze a reaction of) a particular substrate at a *measurable* rate, this is not to say that this same enzyme does not convert that particular substrate AT ALL. Similarly, while a particular enzyme may not have a *measurable* affinity for a particular substrate, this is not to say that this same enzyme does not have ANY affinity. Rate and affinity are relative terms which can only be defined by the ability to assay either a catalytic rate or affinity binding. For example, no binding affinity may be measured using a less sensitive colorimetric assay while some level of affinity may be measured using a more

sensitive radioactive assay. Thus, a previously considered "new" substrate would be merely an "improved" substrate. The delineation of a "new" enzyme substrate is based on assay techniques as well as intrinsic enzyme function. The Examiner recognizes the difficulty in claiming Applicants' intended invention considering this issue of "new" substrate; however, said difficulty is inherent in the subject matter of the invention. Moreover, in view of the field of enzymology, the Examiner is skeptical of the grandiose claims of Applicants in that they can obtain enzymes using wholly "new" substrates. A more reasonable interpretation of the power of the claimed methods is that previously poorly utilized substrates have now been improved since this method of random, undirected point mutations cannot reasonably affect large changes in substrate specificity. For example, an exchange in substrate specificity of methanol to ethanol is reasonable while an exchange in substrate specificity of methanol to urea is unreasonable.

Considering a reasonable concept of the term "new" enzyme substrate, the Examiner has set forth a 103(a) rejection which renders the pending claims unpatentable over Greener et al. in view of Wilks et al.

Although not expressly stated in Greener et al., it can be assumed that Greener et al. did not assay their mutant phosphatase (generated by the mutator strain method) with a substrate which was not considered a substrate for the native phosphatase, i.e. they would have reasonably used a substrate which is catalytically converted to product at a robust rate for ease in assaying activity. Therefore, the Examiner has added a 103(a) rejection to address the concept of assaying a "new" substrate (said concept is unclear in Claim 1 as noted by the 112, second paragraph

rejection above). Said 103(a) rejection includes prior art which teaches the ability to produce "new" enzymes with "new" substrate specificities. Thus, the combination of the method steps of Greener et al. and the "new" substrate production of Wilks et al. would render obvious the assaying of the enzyme produced by Greener et al. with "alternate" or "new" substrates.

Applicants argue that "[t]he present invention as claimed employs a method for inducing substrate specificity changes in enzymes"; the Examiner notes that this is not an accurate description of the methods claimed. The instant methods are *random* mutagenesis methods followed by appropriate screening with "new" substrates. Said method IN NO WAY INDUCES substrate specificity changes; these changes are serendipitous and are subsequently screened for. Greener et al. practice all the method steps claimed except the step which uses a "new" substrate to screen the randomly mutated enzyme; said step is made obvious by Wilks et al.

Applicants argue that Greener et al. have a different intent in practicing their method, i.e. to increase the range of temperatures under which the enzyme can perform catalysis. The intent of Greener et al. in practicing the method steps claimed is not pertinent. Any deficiency relating to assaying using "new" substrates in the method steps is taught by Wilks et al.; Wilks et al. also provides an appropriate motivation for one of ordinary skill in the art.

Applicants argue that Greener et al. have not taught all the elements of the present invention. As noted above

> "Greener et al. teach the introduction of a cloned phosphatase gene into the *E. coli* strain XL1-Red (Stratagene, La Jolla, CA) for the purpose of introducing single, random point mutations into said gene, iterating the process for several

> generations to achieve the appropriate degree of mutation in said gene, and screening for phenotypic variants of said gene in a nonmutator host organism, specifically *E. coli* which is a Gram-negative bacterium (see pages 383-384). The cloned gene specifically used in Greener et al. is alkaline phosphatase which is generally classified in the hydrolase family of enzymes (Enzyme Commission number EC 3.), further classified as an esterase, and as such specifically meets applicants' limitations in claims 5-7. Greener et al. also teach that "[p]resumably, these...mutations [as induced by the mutator strain method] result in a variant having higher specific activity..." (see page 384); this presumption is considered a reasonable conclusion by the Examiner. The term "specific activity", as is well-known in the art and is defined by Fersht, is k_{cat}/K_m. Thus, the method taught by Greener et al. produces an esterase/phosphatase with a new substrate specificity."

Applicants say that Greener et al. teaches an enzyme with the ability the breakdown of a certain indicator substance. This "indicator substance" is a substrate of the enzyme, namely 5-chloro-bromo-3-indolyl phosphate, whose phosphate is hydrolyzed by the enzyme; the indicating nature of the substrate is its blue color for ease in quantitating enzymatic activity. Greener et al. teach that the resultant mutant phosphatase, as assayed in the non-mutator *E. coli* strain which inherently has no "impeding enzymic activity" since the phosphatase is native to *P. furiosus*, has increased specific activity for the 5-chloro-bromo-3-indolyl phosphate substrate. The "new" substrate notion is added by Wilks et al. as described above.

Applicants traverse the rejection of Claims 4 and 10-11 under 35 U.S.C. 103(a) as obvious over Greener et al. in view of Wilks et al. This rejection has been maintained above (limited to Claim 11 alone since 4 and 10 have been included in the 102(b) rejection) with the proviso that the limitation of using a "new" substrate is unclear. A 103(a) rejection has also been set forth

above in anticipation of Applicants' amendments to Claim 1 to clarify the concept of a "new" substrate.

Applicants argue that no *prima facie* case of obviousness has been set forth due to a lack of motivation and sufficient expectation of success. Applicants argue that there is a difference between altering substrate specificity (by Greener et al.) and "creating an entirely new substrate specificity" (in the present invention). As the Examiner has set forth above, this notion of an entirely new substrate specificity is grandiose in the field of enzymology. Moreover, Applicants bolster this claim of differentiation by citing phrases like "randomness" and "likelihood" and "entropy". Previously in prosecution, an enablement rejection was set forth stating that the methods proposed are wholly unpredictable for use in producing the claimed outcome, namely a "new" enzyme. This rejection was withdrawn based on the fact that Greener et al. has accomplished such a feat using the same methods as Applicants. The difference, it appears, between Greener et al. and Applicants' invention is the step of assaying using an alternate substrate which has clearly been made obvious in view of Wilks et al. by (1) adding the deficient element, (2) providing a motivation to combine the references, and (3) providing a reasonable expectation of success that the combination will produce Applicants' invention.

Applicants' comment concerning page number references to Wilks et al. is correct. An incorrect Wilks et al. reference was inadvertently cited on the PTO-892 by the Examiner and attached to a previous Office action. The appropriate citation is "Wilks et al. Alteration of

enzyme specificity and catalysis by protein engineering. Current Opinion in Biotechnology (1991) 2:561-567" which is enclosed herein.

Applicants' traversal regarding this 103(a) rejection is skewed by the incorrect reference citation. Applicants' comments focus on the pessimistic view Wilks et al. suggests for random mutagenesis methods. Clearly, this is not the case in the Wilks et al. reference cited above which *does* equate methods of random mutagenesis/screening and rational design/construction in the first paragraph of the introduction on page 561. While Wilks et al. teach methods of rational enzyme design, this reference is useful for teaching the *ability* to alter substrate specificity and the extent to which such alterations can be achieved (for example, total switch of NADH to NADPH substrate usage). Since Greener et al. would only be deficient in the screening step, as intended to be claimed in Claim 1, Wilks et al. provides said step (albeit inherently in the discussion of switching substrates from NADH to NADPH, for example), a motivation to combine, and a reasonable expectation of success.

Conclusion

11. No claims are allowed in the instant application for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Kathleen M. Kerr whose telephone number is (703) 305-1229. The Examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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April 27, 2001